PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/05, 47/26

A1

(11) International Publication Number: **WO 97/10814**

(43) International Publication Date: 27 March 1997 (27.03.97)

(21) International Application Number: PCT/IB96/00868

(22) International Filing Date: 29 August 1996 (29.08.96)

(30) Priority Data:

2620/95-5	18 September 1995 (18.09.95)	CH
3257/95	17 November 1995 (17.11.95)	CH

(81) Designated States: AU, BR, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(71) Applicant *(for all designated States except US)*: VESIFACT AG [CH/CH]; Jöchlerweg 4, CH-6342 Baar 2 (CH).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: WEDER, Hans, Georg [CH/CH]; Alte Landstrasse 84B, CH-8803 Rüschlikon (CH).

(74) Agents: RYFFEL, Rolf et al.; Hepp, Wenger & Ryffel AG, Friedtalweg 5, CH-9500 Wil (CH).

(54) Title: PROPOFOL NANODISPERSIONS

(57) Abstract

The invention relates to nanodispersions for the intravenous administration of the anaesthetic agent propofolum having lipophilic properties. The nanodispersion is prepared by adding propofolum to an aqueous solution of a partial fatty acid ester of polyoxyethylene sorbitan at low concentrations followed by moderate stirring at room temperature or under moderate heating.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

PROPOFOL NANODISPERSIONS

The following invention relates to nanodispersions for the intravenous administration of an anaesthetic agent having lipophilic properties, a process for the preparation of these nanodispersions and its use in therapeutic methods.

Propofol (propofolum), cf. *Merck Index Tenth Edition (1989), entry No. 7847, page 1245*, chemical name: 2,6-diisopropylphenol, is an intravenous sedative hypnotic agent for use in the induction and maintenance of anaesthesia or sedation. Intravenous injection of a therapeutic dose of propofol produces hypnosis rapidly and smoothly with minimal excitation, usually within 40 seconds from the start of an injection, cf. *Physicians' Desk Reference, 49th Edition 1995, Medical Economics (USA), page 2436.* In various countries the active agent propofol is commercially available only in a single pharmaceutical dosage form, e.g. which is an injectable emulsion marketed under the trade mark Disoprivan® (Stuart, Zeneca). This formulation is an emulsion consisting of soy bean oil, egg lecithin, and glycerol.

Emulsions of this type used as injectables have serious drawbacks: M.Tressler et al. report in *Can. J. Anaesth. 1992, 39 (5 Pt 1), 509-511* of undesirable growth of bacteria in emulsions containing propofol. C. Pirttikangas et al. report in *Intensive Care Med. 1993, 19(5), 209-302* of undesirable immunesuppressive effects resulting from bolus administrations or rapid infusion treatment. M. Lindholm reports in Minerva Anaesthesiol. 1992, 58 (10), pages 875-879 that the maximal lipid clearance is exceeded. *Physician's Desk Reference, loc. cit.*, mention serious adverse reactions, such as bradycardia, apnea, hypotension, and others. A detailed section is dedicated to Warnings, Precautions, and Drug Interactions.

The act of administering the dosage form intravenously is also painful. This may be explained by the lipophilic character of the ingredients of the dosage form. For this reason, the simultaneous administration with analgetics is also recommended. Strict aseptic technique must always be maintained during handling. The detailed restrictions and instructions according to

Physician's Desk Reference, loc. cit., are self-explanatory and indicate the need for an improved formulation.

A suitable intravenous dosage form has not yet been available for the important anaesthetic agent propofol. The object of the present invention, therefore, is to make available a suitable intravenous dosage form for the lipophilic active agent propofol.

The number of approaches for solving the problem according to the present invention by developing suitable alternative dosage form is severely limited, since propofol has to be administered in the course of intensive care to unconscious patients or temporarily handicapped patients. This excludes the use of oral dosage forms, e.g. capsules which appear suitable for formulating lipophilic therapeutic agents. However, the use of such dosage forms requires improved health status of the patient. In a narrower sense, the object of the present invention is the preparation of an improved new intravenous dosage form.

The drawbacks of the known injectable emulsion are explicable by its insufficient homogeneity caused by the lipophilic properties of the additives and the therapeutic agent propofol. Its pronounced lipophilicity especially explains the insufficient suitability for intravenous dosage forms which require the solubilization of the therapeutic agent in the carrier liquid. In order to effect solubilization successfully, the lipophilicity of the active agent also necessitates the addition of larger amounts of pharmaceutical carrier materials. *U.S. Patent Specification No. 4 452 817* discloses a microemulsion containing 1 % propofol, which also contains 10 % of the additive Tween® (ICI) 80. Such a high amount of surfactants in an intravenous dosage form is physiologically inacceptable.

In a narrower sense, the object of the present invention is the preparation of a new, improved intravenous dosage form for the lipophilic agent propofol which contains physiologically acceptable amounts of carrier materials. In the event that the addition of one of the few solubilizers permitted in national pharmacopoeias still fails to promote the solubility of the active agent, the incorporation in finely dispersed systems based on lipid mixtures is suggested

in the prior art. In such systems, the sparingly soluble therapeutic agent is encapsulated in lipid particles of a particle size of less than 1 µm. The "loaded" lipid particles then form with the aqueous carrier liquid an aqueous phase of colloidally dispersed or, preferably, finely dispersed character, which differs from the true homogeneous distribution of solutes at molecularly dispersed level but is, nevertheless, sufficiently homogeneous for the preparation of intravenous and oral dosage forms. Numerous publications suggest the incorporation of therapeutic agents of low solubility in micelles, mixed micelles, reversed micelles, unilamellar or multilamellar liposomes, nanocapsules or nanoparticles.

It has surprisingly been found that the addition of specified amounts of a partial fatty acid ester of polyoxyethylene sorbitan in low concentrations is especially suitable for the preparation of a homogeneous dispersion of small particles in the form of a nanodispersion of the active agent propofol.

The present invention, therefore, relates to a nanodispersion for the intravenous administration of an anaesthetic agent having lipophilic properties, which comprises:
a) 1.0 - 2.0 weight % of the therapeutic agent 2,6-diisopropylphenol (propofolum);
b) 1.0 - 3.0 weight % of a partial fatty acid ester of polyoxyethylene sorbitan;
c) the carrier liquid water, in the degree of purity necessary for intravenous administration;
wherein the weight ratios of component a) to component b) are in the range of 0.33 - 1.2.

The nanodispersion defined above is distinguished by useful phase properties of the solubilized therapeutic agent. For example, where opalescence and transparency occur in incident light, only an extremely slight milky turbidity reveals that the dispersion formed still has physical differences vis-à-vis the ideal state of a true molecular solution. Electron microscope images show that a population of more than 95 % of the sparingly soluble propofol is present in the form of a dispersion of nanoparticles having a particle size of less then 30 nm ("nano-dispersion"). However, these differences vis-à-vis a true solution are acceptable in view of some remarkable homogeneity properties of the nanodispersion. These properties can be made apparent in a high storage stability; for example there is no separation after storage for several

months at 2-8°C (by extrapolation the expected stability is more than two years). A comparison with the conventional injectable emulsion formulation Disoprivan® reveals the following: A sample of Disoprivan® of 1.0 ml contains a mean of about 3.2×10^6 particles having a size of ≥ 1.0 µm and still about 10 to 30 particles having a size of ≥ 25.0 µm, whereas in a sample of 1 ml of the nanodispersion according to the present invention only a small population of up to some thousends particles having a particle size of more than 1 µm is present. Practically no particles having a particle size of more than 25 µm are present. Such particle distribution of extremely few particles of undesirably large sizes is particularly useful and is far below the limits which are acceptable according to the regulations of national regulatory authorities, such as the Food and Drug Administration (FDA) in the U.S..

A preferred embodiment of the present invention relates to a nanodispersion comprising:
a) 1.0 - 2.0 weight % of the therapeutic agent 2,6-diisopropylphenol (propofolum);
b) 1.0 - 3.0 weight % of polyoxyethylene(20)sorbitan monooleate;
c) the carrier liquid water, in the degree of purity necessary for intravenous administration;
wherein the weight ratios of component a) to component b) are in the range of 0.33 - 1.0.

The therapeutic agent propofol - component a) - is present in the nanodispersions defined above in the dose which is approved for injection formulations. According to *Physician's Desk Reference*, *loc. cit.*, an injectable formulation of 1 ml contains a dose of 10 mg.

The partial fatty acid ester of polyoxyethylene sorbitan - component b) consists preferably of a substantially pure ester of sorbitan or a mixture of different esters of sorbitan in which the structure of the fatty acid groups and the length of the polyoxyethylene chains may vary. The hydrophilic sorbitan is preferably etherified by three hydrophilic polyoxyethylene chains and esterified by a hydrophobic fatty acid group. The sorbitan may, however, alternatively be etherified by only one or two polyoxyethylene chains and correspondingly esterified by two or three fatty acid groups. The basic sorbitan structure is altogether substituted by a minimum of two and a maximum of three hydrophilic groups, the term "hydrophilic group" embracing the polyoxyethylene chains, whereas the fatty acid groups are hydrophobic.

The polyoxyethylene chain is linear and has preferably from 4 to 10, especially from 4 to 8, ethylene oxide units. The ester groups on the basic sorbitan structure are derived from a saturated or unsaturated, straight-chain carboxylic acid having an even number of from 8 to 20 carbon atoms. The ester group derived from that carboxylic acid is preferably straight-chained having 12, 14, 16 or 18 carbon atoms, for example n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl. The ester group derived from an unsaturated carboxylic acid having an even number of from 8 to 20 carbon atoms is preferably straight-chained having 12, 14, 16 or 18 carbon atoms, for example oleoyl. The mentioned esters of sorbitan are in conformity with the data given in the British Pharmacopoeia (specialised monograph) or Ph.Helv.VII. In particular, the product specifications published by the mentioned manufacturers with the information on data sheets for the relevant product, especially specifications such as shape, colour, HLB value, viscosity, ascending melting point and solubility, apply.

Suitable partial fatty acid esters of polyoxyethylene sorbitan are commercially obtainable under the trademark Tween® of ICI Corp. and known by the chemical names polyoxyethylene (20 or 4)sorbitan monolaurate (TWEEN 20 and 21), polyoxyethylene(20)sorbitan monopalmitate or monostearate (TWEEN 40 and 60), polyoxyethylene(4 or 20)sorbitan monostearate or tristearate (TWEEN 61 and 65), polyoxyethylene(20 or 5)sorbitan monooleate (TWEEN 80 or 81) and polyoxyethylene(20)sorbitan trioleate (TWEEN 85). In an especially preferred embodiment of the invention, polyoxyethylene(20)sorbitan monooleate (TWEEN 80) is used as component b).

Component c), the carrier liquid water having the degree of purity necessary for intravenous administration is, in accordance with the regulations of national pharmacopoeias, germ- and pyrogen-free.

Excipients suitable for injection purposes are present in the nanodispersion if desired. Suitable excipients are approved by Regulatory Authorities for injection purposes, e.g. glycerol, benzyl

alcohol in the degree of purity prescribed for injection purposes, and also excipients suitable for the production of isotonic conditions, for example ionic excipients, e.g. sodium chloride, or other water-soluble excipients, e.g. sorbitan, mannitol, glucose, lactose or fructose.

The present invention also relates to a process for the preparation of the nanodispersions defined above, which is known *per-se* and which process comprises:

First dissolving component b) - partial fatty acid ester of polyoxyethylene sorbitan - in component c) - water - and thereafter adding to this solution component a) - active agent propofol - in the specified amounts and weight ratios defind above;

and subjecting the nanodispersion obtainable to the following subsequent operations:
addition of a further amount of water as carrier liquid and optionally further water-soluble excipients that are suitable for injection purposes; sterile filtration of the clear nanodispersion; or
sterile filtration and subsequent conversion of the nanodispersion obtainable into a dry preparation, optionally with the addition of water-soluble excipients, and reconstitution of the dry preparation to form an injectable nanodispersion.

According to this method, an especially homogeneous, intravenously administrable nano-dispersion of the therapeutic agent propofol is prepared.

The nanodispersion is prepared by adding the oily phase of pure propofol - component a) - to the aqueous phase containing the component b). This mixture is stirred during 2 to 3 houres using a magnetic stirrer or static mixer. Mixing preferably is effected at room temperature or under moderate heating up to 45°C.

The dispersion obtainable can be defined as a dispersion of colloidal nanoparticles of the sparingly soluble lipophilic active agent propofol, or, more simply, as a nanodispersion. By means of measurements from laser light scattering and electron micrographs, the colloidal nanoparticles present in the nanodispersion can be distinguished from other particles such as

liquid crystals, micelles, inverse micelles or liposomes. For the statistical plurality of more than 95 %, especially more than 99 %, an average particle size of less than 25 nm is typical.

For the identification of the nanodispersions obtainable, methods known *per se* are suitable, for example optical examination: Transparence with slight to intense opalescence of the preparation is easily identifiable (indicates average particle size of less than 50 nm); laser light scattering (determination of the particle size and homogeneity); or electron microscopy (freeze fracture and negative contrast technique).

The necessary amount of water, which must be of the purity prescribed for injectables, can be added to the nanodispersion. This nanodispersion can be directly administered after selecting the filtration method suitable for such types of dispersions, preferably sterile filtration (0.2 μm), for example with a PAL filter (Gelman), and optionally after adding further water-soluble excipients that can be used for intravenous dosage forms. Especially sterile filtration is applicable to separate off all relatively large particles in the nanodispersion having a diameter greater than about 200 nm, as well as floating and solid substances. This yields a nano-dispersion having a high proportion of hydrophilic particles of extremely uniform size.

As an alternative to the preparation of a directly administrable nanodispersion, the nano-dispersion may be converted into a dry preparation, especially into a lyophilisate, which is reconstituted prior to administration by the addition of water. An administrable nanodispersion is obtained again after reconstitution of the lyophilisate. For the preparation of lyophilisates, the addition of so-called builders, such as lactose or mannitol, is customary. These excipients are added in such amounts that after reconstitution of the lyophilisate the nanodispersion to be administered has isotonic properties.

Measured amounts of nanodispersion are introduced, optionally in the form of a concentrate, into containers suitable for a unit dose, for example glass ampoules (vials). The filled containers can be cooled, if desired, to about -40° to -50°C, especially to about -45°C, and

then lyophilised at a pressure of about 0.2 to 0.6 mbar by slowly heating to a final temperature of about 25° to 35°C.

The nanodispersion according to the present invention is particularly useful as injection formulation for intravenous administration for the induction and maintenance of anaesthesia or sedation.

The following examples illustrate the invention; the relevant physico-chemical parameters, such as size and distribution of the nanoparticles (laser light scattering methods in the nm range); number of particles per ml (particle counter according to USP in the µm range), viscosity, and concentrations of the active agent in the formulation are shown in the TABLE attached to the Examples.

Example 1: Formulation for an injectable formulation 10 mg/ml. Percentages are given in weight percent.

1.4 % polysorbatum 60
92.8 % aqua ad inj.
1.0 % propofolum (active substance)
0.5 % benzyl alcohol
4.3 % mannitolum

Polysorbatum 60 is dissolved in water, and the mixture is stirred at 45°C with a magnetic stirrer. To this solution the active substance propofol and benzyl alcohol is given. The mixture is stirred for two to three hours at room temperature with a magnetic stirrer (200-300 rpm) until the mixture appears transparent and weakly opalescent. The clear mixture is then sterile filtered (0.2 µm) and filled into vials under sterile conditions. The vials may be stored at temperatures up to 25°C.

Example 2: Formulation for an injectable formulation 10 mg/ml. Percentages are given in weight percent.

1.4 % polysorbatum 60
92.9 % aqua ad inj.
1.0 % propofolum (active substance)
4.7 % mannitolum

The formulation is prepared in a manner analogous to Example 1 at room temperature. Benzyl alcohol is omitted.

Example 3: Formulation for an injectable formulation 10 mg/ml. Percentages are given in weight percent.

1.4 % polysorbatum 80
92.8 % aqua ad inj.
1.0 % propofolum (active substance)
4.8 % mannitolum

The formulation is prepared in a manner analogous to Example 2 at room temperature.

Example 4: Formulation for an injectable formulation 20 mg/ml. Percentages are given in weight percent.

2.8 % polysorbatum 80
90.4 % aqua ad inj.
2.0 % propofolum (active substance)
4.8 % mannitolum

The formulation is prepared in a manner analogous to Example 3 at room temperature.

Physico-chemical data of injectable formulations according to the Examples compared with the commercial formulation Disoprivan®

TABLE

Example	Batch No. / Size [kg]	Laser-Light-Scattering[1] [nm]	Number of Particles/ml[2]		Viscosity [mPas]	Concentr. Propofol[3] [mg/ml]
1	040	AVG[4] 20.8 ± 7.0	> 1 µm	12 175	1.1	9.8
			> 10 µm	213		
			> 20 µm	26		
	1.0		> 30 µm	11		
2	045	AVG[4] 17.8 ± 5.7	> 1 µm	6 394	1.1	9.9
			> 10 µm	45		
			> 20 µm	4		
	1.0		> 30 µm	1		
3	002	AVG[4] 17.9 ± 5.0	> 1 µm	4 154	1.3	9.6
			> 10 µm	12		
			> 20 µm	0		
	50.0		> 25 µm	0		
4	063	AVG[4] 11.5 ± 4.2	> 1 µm	6 899	1.5	19.8
			> 10 µm	55		
			> 20 µm	0		
	1.0		> 30 µm	0		
Diso-privan®	MP 21 Exp. 0997	AVG[4] 123.8 ± 37.9	> 1 µm	3 163 978	1.6	10.0
			> 10 µm	1 308		
			> 20 µm	24		
			> 30 µm	10		

[1] Nicomp 370 Submicron Particle Sizer;

[2] A3 Particle Counter VS, USP conform/ Examples 1 and 2: mean from 6, Examples 3 and 4: mean from 3, Disoprivan®: mean from 18 measurements;

[3] HPLC; [4] AVG = Gauss-Analysis number weighting particle distribution;

Claims

1. A nanodispersion for the intravenous administration of an anaesthetic agent having lipophilic properties, which comprises:
a) 1.0 - 2.0 weight % of the therapeutic agent 2,6-diisopropylphenol (propofolum);
b) 1.0 - 3.0 weight % of a partial fatty acid ester of polyoxyethylene sorbitan;
c) the carrier liquid water, in the degree of purity necessary for intravenous administration;
wherein the weight ratios of component a) to component b) are in th range of 0.33 - 1.2.

2. A nanodispersion for the intravenous administration of an anaesthetic agent having lipophilic properties, which comprises:
a) 1.0 - 2.0 weight % of the therapeutic agent 2,6-diisopropylphenol (propofolum);
b) 1.0 - 3.0 weight % of polyoxyethylene(20)sorbitan monooleate;
c) the carrier liquid water, in the degree of purity necessary for intravenous administration;
wherein the weight ratios of component a) to component b) are in th range of 0.33 - 1.0.

3. A process for the preparation of a nanodispersion according to claim 1, which comprises:
First dissolving component b) - partial fatty acid ester of polyoxyethylene sorbitan -
in component c) - water - and thereafter adding to this solution component a) - active agent propofolum - in the specified amounts and weight ratios according to claim 1 or claim 2 and stirring this mixture using a magnetic stirrer or static mixer preferably at room temperature or under heating up to 45°C.

4. Nanodispersions of the therapeutic agent 2,6-diisopropylphenol (propofolum) according to claim 1 or claim 2 for use in a therapeutic method by intravenous administration.

5. Nanodispersions according to claim 4 for the induction and maintenance of anaesthesia or sedation by intravenous administration.

INTERNATIONAL SEARCH REPORT

Inten ıal Application No
PCT/IB 96/00868

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/05 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 452 817 (J.B.GLEN ET AL.) 5 June 1984 cited in the application see the whole document	1-5
A	EP,A,0 535 567 (B.BRAUN MELSUNGEN) 7 April 1993 see the whole document	1-5
A	WO,A,95 20943 (KARLSHAMNS) 10 August 1995 see example 18	1-5
A,P	US,A,5 496 537 (R.A.HENRY) 5 March 1996 see the whole document	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 1996	22. 11. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

information on patent family members

Inten ..al Application No
PCT/IB 96/00868

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4452817	05-06-84	GB-A-	1472793	04-05-77
		AU-B-	502164	12-07-79
		AU-A-	7953675	30-09-76
		BE-A-	827290	29-09-75
		CA-A-	1038764	19-09-78
		DE-A-	2513797	09-10-75
		FR-A-	2265357	24-10-75
		HK-A-	34380	01-07-80
		JP-A-	50154410	12-12-75
		NL-A-	7503696	30-09-75
		SE-A-	7503542	29-09-75
		US-A-	4798846	17-01-89
		US-A-	4056635	01-11-77
EP-A-535567	07-04-93	DE-A-	4132677	08-04-93
		DE-D-	59203456	05-10-95
		ES-T-	2077317	16-11-95
WO-A-9520943	10-08-95	AU-A-	1723395	21-08-95
		AU-A-	1723495	21-08-95
		AU-A-	1723595	21-08-95
		CA-A-	2182575	10-08-95
		CA-A-	2182576	10-08-95
		CA-A-	2182577	10-08-95
		NO-A-	963240	02-08-96
		NO-A-	963241	02-08-96
		NO-A-	963242	02-08-96
		WO-A-	9520944	10-08-95
		WO-A-	9520945	10-08-95
		ZA-A-	9500939	09-10-95
		ZA-A-	9500940	09-10-95
		ZA-A-	9500941	09-10-95
		SE-A-	9402454	13-01-96
US-A-5496537	05-03-96	WO-A-	9629052	26-09-96